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PHYSIOLOGICAL ADAPTATIONS TO CARBON MONOXIDE LEVELS AND EXERCISE IN NORMAL MEN

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Physiological Adaptations to Carbon Monoxide Levels and Exercise in Normal Men

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SUMMARY

Normal, young, non-smoking men were studied at rest and during submaximal exercise with carboxyhemoglobin (COHb) levels of about 1% and after breathing CO to raise the COHb level to 8 to 9%. Arterial and mixed venous blood was sampled. CO caused an increase in minute volume and breathing frequency during exercise but not at rest. CO caused no changes in cardiac output, heart rate, lactate, lactate/pyruvate ratio, tidal volume, CO_2 output or 2,3 DPG during rest or exercise. CO caused a decrease in O_2 consumption, in arterial-venous O_2 content difference and in venous O_2 content and venous Po_2 during exercise and in the latter two also at rest. Changes in O_2 affinity are still being calculated.

INTRODUCTION

Carbon monoxide is believed to exert its toxic effect almost entirely through its binding on the active sites of hemoglobin. This reduces the oxygen carrying capacity of hemoglobin and produces a hypoxemia similar to that of anemia. However, the displacement of oxygen from active sites has the equivalent effect of displacing the oxygen dissociation curve of the remaining sites to the left and hence effectively increasing the affinity of the remaining sites for oxygen. This effect has long been known since Haldane[1]. This phenomenon has little effect on arterial oxygenation but has been believed to have a profound effect on oxygenation of tissue and on oxygenation of venous blood. Because of normal arterial Po_2 in CO poisoning, it is generally believed that the body has limited physiological defense against CO compared with the hypoxemia of altitude.

Of the many studies on the effects of carbon monoxide, only Ayres, et al[2,3,4] have directly sampled the blood from the pulmonary arteries. In his studies, observations were made only at rest. In the studies of Vogel, et al[5,6], observations were made at submaximal and maximal exercise. The cardiac output was measured by dye dilution, but a mixed venous sample was not obtained.

This study reports observations made on healthy, young, normal, male subjects under conditions of rest and submaximal work before and after giving a load of carbon monoxide to produce approximately 10% carboxy-hemoglobin concentration. Pulmonary artery blood was sampled. Observations were also done on levels of 2,3 diphosphoglycerate and estimations were made of the oxygen affinity of the hemoglobin, both in vitro and in vivo.

METHODS

Nine, young, male, non-smoking subjects were chosen for study. The physical characteristics of the last seven subjects are shown in Table I. The first two subjects served mainly as pilot studies. A number of pieces of information are missing about both of these. Essentially all of the data desired is available on the last seven subjects, except that one sample of blood from the pulmonary artery was actually a wedge sample and was omitted from the data.

The subjects ate a light breakfast before 6 a.m. and reported to the laboratory about 7 a.m. Blood carboxyhemoglobin was estimated by a method modified slightly from Jones, et al[7]. The subject warmed up for 10 minutes on the stationary constant load bicycle ergometer at a work load of 50% of his estimated maximal O_2 consumption ($\dot{V}o_2$ max). The predicted $\dot{V}o_2$ max. as calculated according to the formula of Armstrong, et al[8] based on age and body weight and the corresponding bicycle load was calculated from the empirical formula:

$$L = 570\ \dot{V}o_2 - 200$$

where L = bicycle load in KPM

$\dot{V}o_2$ = desired O_2 consumption in L/min.

The subject then lay on a bed while a Swan-Ganz[9] catheter was inserted in an antecubital vein in one arm and advanced to the pulmonary artery. A plastic arterial cannula was placed percutaneously in a brachial artery of the other arm. The subject then moved to the bicycle where he remained for the rest of the experiment. After moving, the position of the catheter tip was rechecked. Observations of inspired minute volume and of heart rate were made during a rest period of five minutes, the last three minutes of which samples of expired air, arterial blood and mixed venous blood were obtained. Exercise was then performed at a load

of 75% of the estimated $\dot{V}o_2$ max. for a period of 5 minutes. Heart rate, ECG, respiratory rate and inspired minute volume was observed for the entire period. Mixed venous and arterial blood samples were obtained during the last two minutes of exercise and expired air was collected for the last minute of exercise.

The subjects were then loaded with carbon monoxide, first to about 7% carboxyhemoglobin, and then to 10% carboxyhemoglobin by breathing a measured volume of 1% carbon monoxide in air. The dose was calculated according to the formula of Pitts and Pace[10]. After a period of from 20 to 45 minutes, the studies at rest and exercise were repeated as described for control state. During the exercise period, the subject breathed air containing 60-70 ppm CO. Following the second exercise study the catheter was withdrawn and the subject breathed 100% oxygen for approximately 30 minutes. A few of the subjects experienced a mild phlebitis and thrombosis in the vein the cardiac catheter had been placed in. All the subjects were able to complete the protocol except one, K.S., who passed out and would have fallen from the bicycle after 4 minutes and 40 seconds of exercise. The subjects knew the protocol. Several of them stated that the second exercise period was easier than the first.

Blood samples were measured for pH, Po_2 and Pco_2 using radiometer electrodes and Model PHM72 readout system. Expired air volume was measured in a large spirometer and a sample taken for analysis by the micro-Scholander method. Blood was analyzed for O_2, CO_2 and CO content by the method of Van Slyke. Hemoglobin concentration was measured as cyanmethemoglobin photometrically. Lactate and pyruvate were 2,3 diphosphoglycerate was determined by specific enzymatic methods using commercial kits.*

* Lactate and pyruvate were determined by use of kits from Boehringer Mannheim and 2,3 DPG by using a kit from Calbiochem.

Blood was equilibrated in a swirl tonometer with approximately 3% and 4% oxygen and 5% CO_2 in nitrogen, respectively; and oxygen content, Po_2, Pco_2 and pH were determined as described above. The cardiac output was calculated from the Fick equation and in vitro and in vivo P_{50} will be computed from the data of the mixed venous sample by methods to be developed. The difference between means of control and after CO was tested for statistical significance by student's "t" test for paired data.

The base excess of the extracellular fluid was computed according to Collier, Hackney and Mohler[11].

RESULTS

Table II contains a summary of the most pertinent data obtained. The mean and standard deviation is shown for all data obtained. The mean carboxyhemoglobin concentration was 8.9% after loading and during exercise this lowered slightly to 7.8% even though 60 to 70 ppm of carbon monoxide was breathed during the exercise period. There was a significant increase in minute volume during exercise after CO. This was due entirely to an increase in respiratory frequency as the tidal volume did not change significantly. The increase in minute volume during exercise caused a slight lowering of the arterial Pco_2, but the change was not statistically significant. There were no significant changes in arterial Pco_2 caused by carbon monoxide. However, the mixed venous Po_2 was significantly lowered at both rest and during exercise, being lowered to 2[illegible] torr during exercise after CO. The lowest mixed venous Po_2 observed was 20 torr on two occasions. The alveolar-arterial oxygen tension difference was increased during both rest and exercise. The difference was not significant during exercise but was during rest. This may have been due to observation during an unsteady state from the previous exercise.

The arterial oxygen content was, of course, lowered as this was essentially a manipulated variable. The mixed venous oxygen content, however, was also significantly reduced, being approximately 1 volume % lower than the control. However, the arterial-venous oxygen content difference was also lowered by CO during both rest and exercise. The change caused by CO was not statistically significant at rest but was statistically significant during exercise. This was made possible not by a change in blood flow which did not change significantly due to CO during either rest or exercise but was caused by a reduction in oxygen consumption during exercise. There were no statistically significant changes in CO_2 output but there was slight drop after CO during exercise so the respiratory exchange ratio was essentially unchanged. There were no significant changes in lactate, pyruvate, or lactate/pyruvate ratios caused by CO during exercise. The changes observed after CO at rest were probably related to the first exercise period. There were no significant changes in DPG caused by either CO or exercise.

Table III shows the results of some of the most pertinent acid-base data for arterial and venous blood. The lactate values are again shown in this table but in meq./L, for comparison with the acid-base data. Fig. 1 shows the arterial and venous acid-base measurements at rest and during exercise.

DISCUSSION

The reduction in oxygen consumption which was observed after CO during exercise was also observed during maximal 3 minute exercise in an earlier study in our laboratory[12] but not observed during submaximal 3 minute exercise. It may be that some of our subjects were close to $\dot{V}o_2$ max.

One of our subjects, K.S., exercised at $\dot{V}o_2$ max. because he was unable to complete the work. Our empiric formula for computing the bicycle load may have given too high a work load. In comparison with the formula of Cotes[13], our subjects were working at about 84% of $\dot{V}o_2$ max. and if compared with Astrand and Rodahl[14] were working at 87% of $\dot{V}o_2$ max., rather than at the expected 75%. This reduction in oxygen consumption which is observed after CO during exercise seems tenable only if we assume that there is an increase in oxygen debt because it does not seem logical that carbon monoxide would cause an increase in mechanical efficiency. However, this could not be absolutely ruled out without further study.

A reduction in oxygen consumption after CO was also reported by Chevalier, et al[15]. The total amount of oxygen consumed before CO for 5 minutes of exercise was 5.99 L. (an average of 10 subjects) and after CO the same workload required only an extra 5.79 L. This difference was not significant but neither was the oxygen debt which was 1.65 L. control and 1.84 L. after CO. However, the percentage of the oxygen debt of the total, or the sum of these two was significant at the 5% level. The sum of O_2 consumed during work plus the O_2 debt is identical before and after CO.

Three other studies do not report a change in oxygen consumption during exercise. Asmussen and Chiodi[16], reporting on 3 subjects, and Klausen, et al[17], reporting on 8 subjects, both showed no difference in oxygen consumption. Vogel, et al[5] reported that there was no difference in oxygen consumption at the same work load and shows a graph on which oxygen consumption is plotted against work load for a number of individuals. In view of our data, it might be well to look at the individual cases in his study.

The cardiac output which we found unchanged was also reported unchanged by Asmussen and Chiodi[16] and by Klausen, et al[17]. However, in their studies the cardiac output was measured by an indirect "bloodless" method. The acetylene method was used by the first group and a CO_2 rebreathing method by the second. Vogel, et al[6], using the dye-dilution method, report that there is an increase in cardiac output for submaximal exercise. However, in Vogel's presentation, he plotted the cardiac output as a function of oxygen consumption rather than as workload. If there were small reductions in oxygen consumption at the same workload, this might change the data somewhat. Vogel's subjects were at a higher COHb (about 20%) and the difference in response of cardiac output probably represents a true difference in response at the higher CO load. Chiodi, et al[18] found an increase in cardiac output at high CO levels but no increase at lower CO levels.

The dye-dilution method which Vogel used gives approximately the same value for cardiac output as the direct Fick method in patients at rest or during mild exercise[19] but has not been adequately compared at high workloads in normals. The normal data of Tabakin, et al[20] using dye dilution and treadmill exercise gives higher cardiac outputs at a given work load than the data of Reeves, et al[21] using the direct Fick. Our subjects show only slightly higher cardiac outputs than those of Reeves. Even though the direct Fick method may be preferable to the dye-dilution method at heavy exercise, the difference in methods probably does not account for the difference in response of cardiac output to CO in our two studies.

The heart rate which we found unchanged was found to be increased by most other observers[6,10,16,17,22]. However, Chevalier, et al[15] report a

reduction in heart rate during exercise following CO inhalation. Another study in our laboratory[11] also showed no change in heart rate after CO. In our first study, the subjects were sham loaded in a single blind procedure; but in the present study, the subjects knew that the CO load followed the control study. The ECG showed no changes after CO at rest or exercise. This was also found in the young subjects of Fortuin, et al[22].

The alveolar-arterial Po_2 difference was quite high in all of our subjects, perhaps because they tended to hyperventilate. CO caused an increase in this difference which was statistically significant at rest. Brody and Coburn[23] first reported this phenomenon which is due to the decrease in mixed venous Po_2 and O_2 content after CO.

The acid-base data given in Table III shows that the acid-base changes are mostly due to lactate production during exercise. Neither lactate production nor acid-base changes are affected by the CO load. The lactate concentration at rest after CO was elevated but this is probably because the resting sample after CO was taken from 38 to 73 min. (average 59 min.) after the first exercise and the lactate had not yet been metabolized to control values. Asmussen and Chiodi[16] reported an increase in lactate production during exercise caused by CO but their COHb levels were 20-30%.

Visser, et al[24] have investigated the relation between lactate and arterial blood acid-base changes following acute exercise and found that the change in blood lactate was almost identical with the change in plasma bicarbonate concentration corrected for changes in Pco_2. (This change is essentially the change in base excess of the arterial plasma (BE_p).) The addition of lactic acid to in vitro blood gives a lesser change in BE_p, making it necessary to postulate some unknown acids in the body. There are two errors in this analysis which have been

clarified by more recent work. First, the correction for changes in Pco_2 was based on an in vitro CO_2 dissociation slope for blood. Because of dilution effective of the buffer value of blood with interstitial fluid, the ECF has a buffer value which is about 1/3 of that of blood. Thus if there was a change in Pco_2 during exercise in his patient population, Visser would have calculated a false change in base. We have obviated this by calculating the base excess of the ECF[11]. Second, inspection of figure 1 shows that the exchange of CO_2 from venous to arterial blood is along an in vitro blood slope and not along the ECF or in vivo slope. This is due to the fact that the pulmonary capillary exchange is only with the blood and does not include an appreciable interstitial fluid pool. This relationship was first stated by Roos and Thomas[25]. This fact makes it necessary to use the mixed venous blood for such comparison. Arterial blood can be used only if the A-V $[HCO_3^-]$ difference is constant in the two situations. This is certainly not true when comparing rest and exercise. Figure 1 and Table IV show the much greater change in base excess of arterial blood than of mixed venous blood. The close equimolecular correlation of lactate and base deficit is only fortuitous and has no scientific basis. There seems to be no need in searching for other sources of acid.

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Table I VITAL DATA ON SUBJECTS STUDIED

Subject	Age	Weight	Height	Body Surface Area
	yr.	kg.	cm.	M^2
AR	34	81.6	170	1.93
SG	22	75.7	169	1.86
RA	27	70.3	179	1.88
KS	23	72.6	183	1.94
JB	30	68.0	175	1.83
JS	19	66.7	170	1.77
VS	21	96.8	189	2.24

Table II MEASURED AND COMPUTED DATA

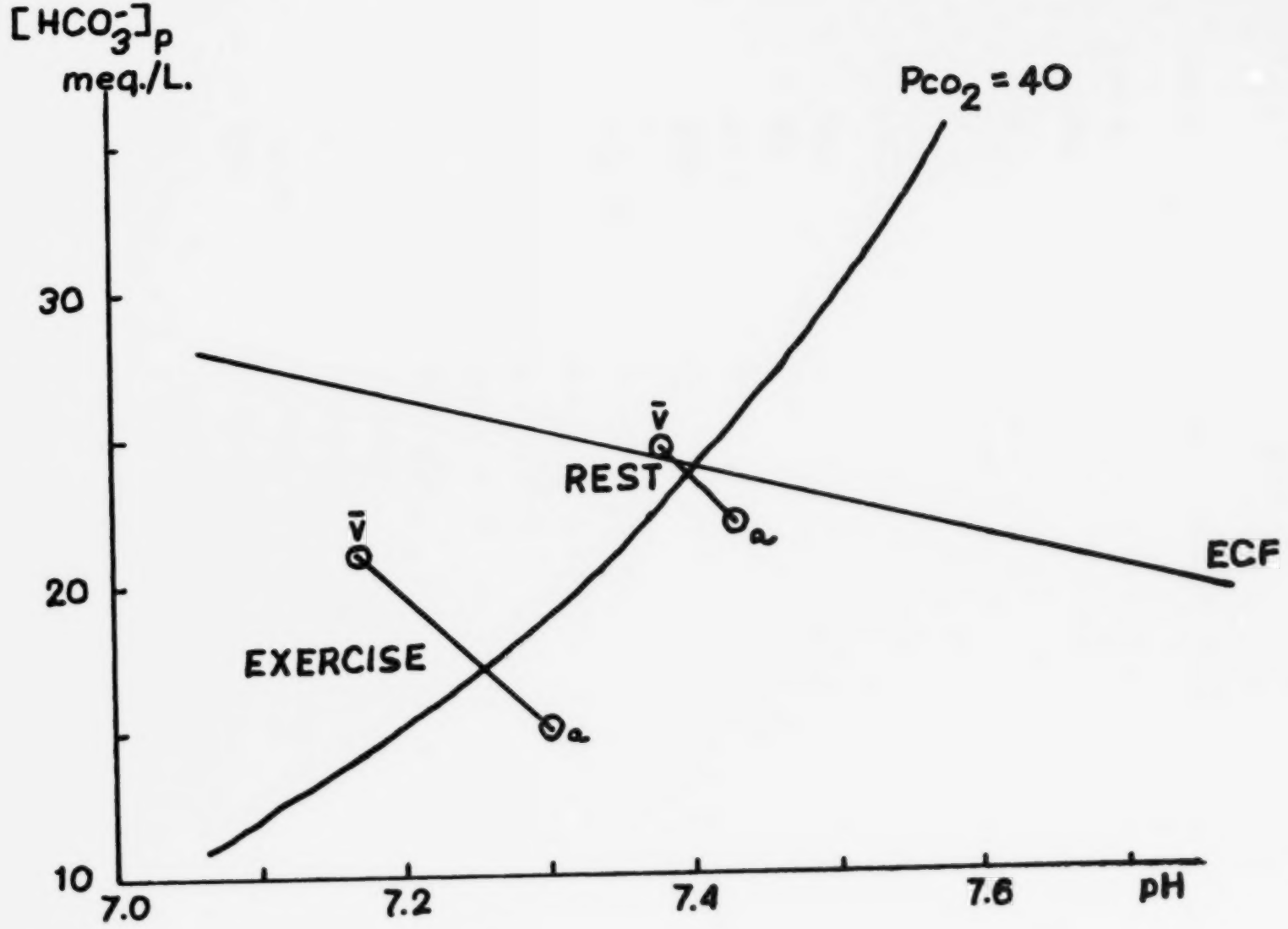
	Units	REST					EXERCISE				
		Control		After CO			Control		After CO		
		Mean	S.D.	Mean	S.D.	P	Mean	S.D.	Mean	S.D.	P
COHb	%	1.1	0.6	8.9	1.7	-	0.9	0.6	7.8	1.0	-
$\dot{V}_E$	L/min	12.9	4.7	15.2	4.9	N.S.	112.5	24.4	120.8	23.4	<0.01
f	/min	13.5	3.9	17.0	5.8	N.S.	37.5	9.4	44.2	8.0	<0.05
V_T	L	0.97	0.29	0.98	0.46	N.S.	3.06	0.51	2.85	0.23	N.S.
$Paco_2$	torr	34.0	5.7	32.0	6.5	N.S.	31.0	2.5	29.4	3.5	N.S.
Pao_2	torr	86.3	8.0	85.3	8.3	N.S.	93.0	4.7	92.0	7.1	N.S.
A-a Do_2	torr	23.4	5.4	26.0	6.2	<0.05	26.6	3.9	29.7	4.5	N.S.
$P\bar{v}o_2$	torr	35.9	1.7	31.4	2.2	<0.01	25.9	2.2	22.2	1.8	<0.01
Cao_2	vol %	18.9	1.2	17.4	0.9	-	20.1	1.1	18.4	0.8	-
$C\bar{v}o_2$	vol %	12.9	1.3	11.9	1.6	<0.1	7.0	1.3	5.9	1.4	<0.005
$Cao_2-C\bar{v}o_2$	vol %	5.9	1.0	5.5	1.2	N.S.	13.1	0.6	12.4	0.7	<0.01
$\dot{V}o_2$	L/min	0.35	0.06	0.38	0.07	N.S.	2.83	0.37	2.74	0.31	<0.05
$\dot{Q}$	L/min	6.0	0.9	7.2	1.9	N S.	21.6	3.0	21.1	3.9	N.S.
f_H	/min	81	13	104	15	<0.02	181	9	177	23	N.S.
$\dot{V}co_2$	L/min	0.32	0.09	0.34	0.09	N.S.	3.29	0.38	3.24	0.30	N.S.
R		0.90	0.15	0.90	0.17	N.S.	1.17	0.09	1.19	0.06	N.S.
Lactate	mg %	18.9	5.7	30.4	12.6	<0.02	92.7	16.2	92.4	17.1	N.S.
Pyruvate	mg %	0.92	0.95	1.60	1.33	<0.05	2.38	2.02	2.05	1.70	N.S.
Lact./pyr. ratio		30.0	13.5	32.5	31.5	N.S.	56.8	30.4	75.2	57.8	N.S.
2,3 DPG	mg/gm.Hb	11.7	3.1	12.7	3.8	N.S.	12.5	3.9	12.7	3.5	N.S.

Table III ACID-BASE AND LACTATE DATA

	Units	REST					EXERCISE				
		Control		After CO			Control		After CO		
		Mean	S.D.	Mean	S.D.	P	Mean	S.D.	Mean	S.D.	P
Arterial											
Pco_2	torr	34.0	5.7	32.0	6.5	N.S.	31.0	2.5	29.4	3.5	N.S.
pH		7.43	0.04	7.43	0.07	N.S.	7.31	0.04	7.31	0.02	N.S.
$[HCO_3^-]_p$	meq./L	22.3	1.9	20.6	1.3	<0.02	15.3	2.1	14.7	1.1	N.S.
BE_{ECF}	meq./L	-1.5	1.7	-3.2	1.0	<0.02	-9.8	2.3	-10.4	1.2	N.S.
Mixed Venous											
Pco_2	torr	40.6	5.1	38.4	5.2	N.S.	57.9	4.6	55.0	4.7	N.S.
pH		7.40	0.03	7.39	0.05	N.S.	7.19	0.05	7.18	0.03	N.S.
$[HCO_3^-]_p$	meq./L	24.6	1.7	22.6	1.3	<0.02	21.3	1.3	20.0	1.4	N.S.
BE_{ECF}	meq./L	0.4	1.6	-1.5	1.3	<0.02	-5.2	1.8	-6.7	1.3	<0.05
Lactate	meq./L	2.1	0.6	3.4	1.4	<0.02	10.3	1.8	10.3	1.9	N.S.

Table IV CHANGES IN ACID-BASE AND LACTATE PRODUCED BY EXERCISE

	Control (Exercise - Rest) meq./L	After 30 (Exercise - Rest) meq./L
Δ Lactate	+8.2	+6.9
BE_{ECF} Venous	-5.6	-5..
Δ BE_{ECF} Arterial	-8.3	-7.2


[HCO3-]p
meq./L.
Pco2 = 40
30
20
10
REST
EXERCISE
ECF
7.0
7.2
7.4
7.6
pH

LEGENDS

Table I	Vital data on subjects studied
Table II	Measured and computed data
COHb	% saturation of Hb with CO
$\dot{V}_E$	Expired minute volume
f_R	Respiratory frequency
V_T	Tidal volume
$Paco_2$	Arterial Pco_2
Pao_2	Arterial Po_2
$\bar{P}vo_2$	Mixed venous Po_2
A-a Do_2	Alveolar-arterial Po_2 difference
$\dot{Q}s/\dot{Q}t$	Total effective R to L shunt as % of total blood flow
Cao_2	Arterial O_2 content
$\bar{C}vo_2$	Mixed venous O_2 content
$\dot{V}o_2$	O_2 consumption
$\dot{Q}$	Cardiac output
f_H	Heart rate
$\dot{V}co_2$	CO_2 output
R	Respiratory exchange ratio
2,3 DPG	2,3 Diphosphoglycerate concentration
S.D.	Standard deviation
P	Probability that the difference between the means before and after CO is due to chance
N.S.	No statistically significant difference
Table III	Acid-Base and Lactate Data
$[HCO_3^-]_p$	Calculated concentration of bicarbonate in the plasma
BE_{ECF}	Base excess of extracellular fluid

Table IV	Changes in Acid-Base and Lactate Produced by Exercise
	(Differences between average data of Table III)
Figure 1	Average acid-base data for rest and exercise before CO
$\bar{v}$	Mixed venous blood
a	Arterial blood
ECF	Average normal non-bicarbonate buffer line for extracellular fluid in humans